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## **ACVIM consensus update on Lyme borreliosis in dogs and cats**

Littman, M P ; Gerber, Bernhard ; Goldstein, R E ; Labato, M A ; Lappin, M R ; Moore, G E

**Abstract:** An update of the 2006 American College of Veterinary Internal Medicine (ACVIM) Small Animal Consensus Statement on Lyme Disease in Dogs: Diagnosis, Treatment, and Prevention was presented at the 2016 ACVIM Forum in Denver, CO, followed by panel and audience discussion and a drafted consensus statement distributed online to diplomates for comment. The updated consensus statement is presented below. The consensus statement aims to provide guidance on the diagnosis, treatment, and prevention of Lyme borreliosis in dogs and cats.

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## ACVIM consensus update on Lyme borreliosis in dogs and cats

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## KEYWORDS

*Borrelia*, coinfection, C<sub>6</sub>, glomerulonephritis, Osp, tickborne

**Abbreviations:** Bb, *Borrelia burgdorferi* sensu stricto; Bb-sl, *Borrelia burgdorferi* sensu lato; BMDs, Bernese Mountain Dogs; CIC, circulating immune-complexes; EBM, evidence-based medicine classification; ICGN, immune-complex glomerulonephritis; LB, Lyme borreliosis; Osp, outer surface protein (eg, OspA, OspC, OspF); PLN, protein-losing nephropathy; TBD, tickborne disease(s); UPC, urine protein/creatinine ratio; VlsE, variable major protein-like sequence, expressed.

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## 1 | INTRODUCTION

Over the past decade, since the first ACVIM Small Animal Lyme Consensus Statement<sup>1</sup> was written, a broader understanding of the large number of *Borrelia* species that exist, the variability of strains of *Borrelia burgdorferi* sensu stricto (Bb), and the diversity of other pathogens carried by *Ixodes* and other ticks has been gained. The geographic distribution of infected ticks has expanded because of bird migration,

suburban sprawl, and climate changes. Additional diagnostic tests are available to help rule out coinfections and other causes of clinical signs potentially attributable to Lyme borreliosis (LB), help differentiate vac-  
cinal from natural acute or chronic exposure anti-Bb antibodies, and follow those antibodies that may wane post-treatment. Guidelines are offered for management of nonclinical nonproteinuric Bb-seropositive dogs and those with suspected clinical Lyme arthritis, Lyme nephritis, or both. Prevention updates include discussion of acaricide products provided as collars, topicals, or chewables that may facilitate owner compliance as well as new vaccination updates.

What has not changed is the finding that most Bb-seropositive dogs and cats show no clinical signs of illness, neither experimentally (using the natural tick exposure model) nor in the field. Signs of Lyme arthritis, seen in a small subset of infected dogs, are transient or respond quickly to PO antibiotics. Signs of dermatologic, neurologic, or cardiac manifestations as seen in human patients are rare and not well-documented in dogs or cats. The most serious (putatively associated) form of LB in dogs, Lyme nephritis, is less common than Lyme arthritis. No experimental model to study its pathogenesis, treatment, and prevention in over-represented (retriever) breeds has been developed, and no validated staining techniques are available to prove that glomerular immune-complexes are Lyme-specific in kidney biopsy specimens from living dogs. Despite these limitations, strategies for empirical management of Lyme nephritis are given, as recently offered by the International Renal Interest Society (IRIS) Glomerular Disease Study Group.<sup>2–5</sup>

The objectives of this consensus statement are to review the evidence and provide findings and recommendations that address these topics regarding *Borrelia* spp. infection in dogs or cats:

1. What species are most common and where are the endemic areas?
2. What are the most common clinical manifestations of LB?
3. What diagnostic tests to confirm Bb exposure are recommended for clinically ill animals?
4. What treatments are recommended for clinically ill animals?
5. What testing is recommended for healthy animals?
6. Should treatments be offered for nonclinical, nonproteinuric seropositive dogs?
7. What prevention modalities are recommended?

This Lyme consensus update is best read in conjunction with the previous one,<sup>1</sup> which includes many of the references for the original experimental and field studies. The update initially was discussed during a Special Interest Group presentation at the ACVIM National Forum in 2015. The authors conversed by phone and community emails with draft findings presented at the ACVIM National Forum in 2016. The 6 authors each voted whether or not to support the summary statements in the update. If a vote is not recorded with a statement, then the vote of support was unanimous. For statements about which a consensus could not be reached, the vote of the committee members is listed and a brief explanation given for the dissenting votes. The update then was provided to the general ACVIM and ECVIM memberships and the Companion Animal Parasite Council and comments considered before

submission for publication. The evidence-based medicine (EBM) scale for references, comments, and recommendations was used as data was obtained from the following:

EBM-A: Randomized, controlled clinical trials in the target species with spontaneous disease.

EBM-B: Randomized, controlled studies in the target species with disease in an experimental setting.

EBM-C: Nonrandomized clinical trials, multiple case series, other experimental studies, and important results from uncontrolled studies.

EBM-D: Expert opinion, case reports, or studies in other species.

## 2 | TOPIC 1: WHAT SPECIES ARE MOST COMMON AND WHERE ARE THE ENDEMIC AREAS?

### 2.1 | Topic 1a: Update on *Borrelia* spp. and associated ticks

There are at least 52 *Borrelia* species,<sup>6</sup> including 21 in the LB group (*B. burgdorferi* sensu lato; Bb-sl; these gram-negative spirochetes generally migrate within the host interstitially), 29 in the relapsing fever group (migrating hematogenously), and 2 undetermined members. In dogs residing in North America, LB has only been associated with *B. burgdorferi* sensu stricto (Bb), of which at least 30 subtypes or strains exist, based on outer surface protein C (OspC) genotyping.<sup>7</sup> The strains appear host-specific; different strains are more common in people as compared with dogs.<sup>7,8</sup> In Europe, coinfections of Bb with other Bb-sl strains (ie, *B. garinii*) may predispose dogs to illness.<sup>9</sup> Other Bb-sl species causing human LB (ie, *B. mayonii*<sup>10</sup> in upper Midwestern states; *B. afzelii*, *B. bavariensis*, *B. garinii*, and *B. spielmanni* in Europe<sup>9</sup>) are not known to cause illness in dogs. The main tick vector for Bb is the 3-host tick *Ixodes scapularis* in Northeastern, Mid-Atlantic, upper Midwestern states, and adjacent areas of Canada<sup>11,12</sup> (<http://www.captvet.org/parasite-prevalence-maps>. Accessed January 5, 2018); *I. pacificus* in the Pacific states and Canada; and, *I. ricinus* in Europe. *Ixodes scapularis* also may transmit *B. mayonii*<sup>10</sup> in the upper Midwest and adjacent Canada causing LB signs (with unusually high spirochetemia) and *B. miyamotoi*<sup>13,14</sup> in the Northeastern, Mid-Atlantic, upper Midwestern US and adjacent areas of Canada is a cause of tickborne relapsing fever (TBRF) in humans but is not yet known in dogs. Similarly, *B. lonestari*<sup>15,16</sup> transmitted by *Amblyomma* and other ticks, once thought to cause southern tick-associated rash infection (STARI) in humans, has not been associated with illness in dogs. Relapsing fever *Borrelia* species (*B. hermsii* in Northwestern states and adjacent Canada;<sup>17</sup> *B. turicatae* in Southern states;<sup>18,19</sup> *B. persica* in the Middle East and Asia<sup>20,21</sup>) have been described in sick dogs (*B. persica* also is described in sick cats), and are transmitted by *Ornithodoros* soft argasid ticks, which only feed for 15–90 minutes.

Most *Borrelia* species are transmitted transstadially within the tick; some in the relapsing fever group<sup>22</sup> (eg, *B. miyamotoi*<sup>23</sup>) also are

transmitted transovarially. *Ixodes* larvae acquire Bb during their first meal, usually in the summer,<sup>24</sup> from a small mammal or bird. The spirochete has numerous outer surface proteins (osp), and during feeding, OspA, expressed by Bb and acting as a hook to the tick's midgut, is down-regulated as OspC expression increases, allowing spirochetes to migrate from the midgut and enter the host, usually after 36–48 hours of tick attachment.<sup>25</sup> More than 30 OspC genotypes or strains are found in nature (not all are pathogenic). Among 16 strains found in New England, the most common ones in humans were types A, B, I, K, and N, whereas the most common ones in dogs were A, B, F, I, and N.<sup>7</sup> This finding impacts vaccine development for humans and dogs.

Other organisms transmitted by *I. scapularis* and potentially associated with clinical illness in humans, dogs, and cats (some agents) include *Anaplasma phagocytophilum*,<sup>26</sup> *Ehrlichia muris*,<sup>27</sup> tickborne encephalitis (Powassan) virus,<sup>28</sup> *F. tularensis*, and possibly *Bartonella* spp.<sup>29,30</sup> These infections can mimic LB and if coinfections occur, may be associated with increased morbidity.<sup>31</sup> Additional *Ixodid* organisms causing illness in humans (eg, *Babesia microti*, *Babesia duncani*, *B. miyamotoi*, and *B. mayonii*) have not yet been associated with disease manifestations in dogs or cats. A *Babesia microti*-like organism causes protein-losing nephropathy (PLN) in dogs in Spain and Portugal and has been found in foxes in North America.<sup>32,33</sup>

Statement: The panel recommends further research to evaluate disease manifestations in dogs and cats because of non-Bb *Borrelia* spp. [EBM-D] Coinfections must be considered in those with suspected LB [EBM-C].

## 2.2 | Topic 1b: Geographic distribution and epidemiology of Bb infection

The geographical persistence and spread of Bb is related to the 2-year, 3-stage (larva, nymph, and adult) life cycle of its *Ixodes* spp. vector, which feeds on a variety of hosts. One blood meal occurs per stage, and uninfected tick larvae hatch to feed on *Borrelia*-infected reservoir hosts, principally mice, squirrels, shrews, birds (*I. scapularis*) and lizards (*I. pacificus*).<sup>22</sup> Within endemic geographical areas, the prevalence of *B. burgdorferi* in nymphal or adult ticks can reach approximately 50%.<sup>34–36</sup> Although nymphs are likely responsible for the majority of Bb transmission to humans and dogs because the small size of this stage allows them to feed on the host undetected, dogs may be less susceptible to transmission of Bb from infected nymph versus adult infected ticks.<sup>37,38</sup> *Borrelia* infection often occurs in the warmer months as a result of the questing behavior of ticks and the recreational habits of humans (owners) and their dogs.<sup>39</sup> Later the same summer, nymphs molt to adults which feed on large mammals, preferentially deer, but also dogs and humans. Adult *Ixodes* ticks can be active in the fall, winter, and early spring when ambient air temperatures exceed 4°C (40°F).<sup>40</sup> Deer are important for the maintenance, amplification, and spread of the tick population because adult ticks mate on them.<sup>22</sup> Thus, *Borrelia*-infected ticks may first spread large distances by bird travel but then spread in a local area by deer or other reservoir movement. With suitable vegetation and

ample reservoir hosts, Bb-infested ticks gradually will become established in an area. Similarly, decreases in vegetation and reservoir hosts, particularly deer, will result in a gradual decrease in disease.<sup>41</sup>

Prevalence estimates of LB in dogs are hindered by a lack of demonstrative clinical signs and no national surveillance system for companion animal diseases. However, screening tests for Bb antibodies are widely used, and estimated canine Bb seroprevalence data at the US state and county and Canadian province and territory levels are available based on input from commercial diagnostic laboratories through the Companion Animal Parasite Council (CAPC; <http://www.capcvet.org/parasite-prevalence-maps>. Accessed on January 5, 2018; Table 1). Lyme disease in humans has been a notifiable disease in the US for many years although not every case is reported to the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention. CDC provides estimate of Americans diagnosed with LB each year. <http://www.cdc.gov/media/releases/2013/p0819-lyme-disease.html>. Press release August 19, 2013. Accessed on January 5, 2018. Reported cases of LB by state or locality, 2006–2016. Available at [www.cdc.gov/lyme/stats/chartstables/reportedcases\\_statelocality.html](http://www.cdc.gov/lyme/stats/chartstables/reportedcases_statelocality.html). Accessed on January 5, 2018.) and surveillance summaries lag behind disease reporting. Underreporting of cases in humans is more likely in highly endemic areas, whereas misclassification (overreporting) is more likely in nonendemic areas.<sup>42</sup> The same may be true for dogs. Travel history of sick or seropositive dogs is an important historical question because cases in nonendemic areas may occur after travel to or importation from endemic disease areas.

The main vector for Bb-sl in Europe is *I. ricinus* and the distribution of LB follows its expansion.<sup>43</sup> The highest prevalence was found in central Europe with an increase of the infection rate of adult ticks from west to east. At least 5 species (*B. afzelii*, *B. garinii*, *B. burgdorferi* s.s., *B. spielmanii*, and *B. bavariensis*) cause disease in humans.<sup>43</sup> Different species are found in questing ticks in different parts of Europe.<sup>44</sup> These different species lead to a wider variety of clinical signs in infected humans in Europe compared with North America; whether or not this is true for dogs is unknown.

Statement: LB is established in geographical areas in North America and Europe, and is spreading, because of persistent tick vectors and reservoir hosts [EBM-C]. The estimated seroprevalence rates in dogs cannot be used as estimates of LB because most dogs that are exposed seroconvert, but do not develop clinical illness [EBM-C].

## 3 | TOPIC 2: WHAT ARE THE MOST COMMON CLINICAL MANIFESTATIONS OF LB?

### 3.1 | Topic 2a: Considerations for dogs in North America

Most Bb-seropositive dogs show no clinical signs. The 2 main clinical manifestations of Bb infection in dogs, Lyme arthritis (in the field and experimentally) and Lyme nephritis (only in the field), were extensively reviewed previously and are not presented in detail here.<sup>1,45–47</sup>

**TABLE 1** Bb antibody seroprevalence totals in dogs in North America, 2017 (<http://www.cpcvet.org/parasite-prevalence-maps>. Accessed on January 5, 2018)

State	#Positive/#tested; %	State	#Positive/#tested; %	State	#Positive/#tested; %
AL	122/37,125; 0.33	KY	666/50,644; 1.32	ND	591/12,804; 4.62
AK	3/59; 5.08	LA	33/17,017; 0.19	OH	2,687/214,195; 1.25
AZ	208/42,740; 0.49	ME	11,856/84,812; 13.98	OK	118/36,923; 0.32
AR	41/19,657; 0.21	MD <sup>a</sup>	11,832/172,014; 6.88	OR	129/12,862; 1.00
CA	1,389/156,151; 0.89	MA <sup>a</sup>	38,448/248,335; 15.48	PA <sup>a</sup>	44,475/318,946; 13.94
CO	188/21,876; 0.86	MI	3,477/238,240; 1.46	RI <sup>a</sup>	2,782/21,696; 12.82
CT <sup>a</sup>	22,132/135,483; 16.34	MN <sup>a</sup>	11,524/137,235; 8.40	SC	748/61,934; 1.21
DE <sup>a</sup>	1,600/29,289; 5.46	MS	27/10,498; 0.26	SD	59/6,809; 0.87
DC <sup>a</sup>	1,069/11,496; 9.30	MO	204/61,677; 0.33	TN	455/59,693; 0.76
FL	1,548/209,288; 0.74	MT	13/1,038; 1.25	TX	584/221,599; 0.26
GA	349/95,670; 0.36	NE	43/7,465; 0.58	UT	11/640; 1.72
HI	22/7,869; 0.28	NV	16/3,345; 0.48	VT	4,724/32,657; 14.47
ID	5/632; 0.79	NH <sup>a</sup>	10,405/78,309; 13.29	VA <sup>a</sup>	21,141/270,527; 7.81
IL	7,003/232,469; 3.01	NJ <sup>a</sup>	16,017/154,178; 10.39	WA	37/4,957; 0.75
IN	3,432/102,541; 3.35	NM	39/9,620; 0.41	WV	2,870/35,058; 8.19
IA	2,606/64,430; 4.04	NY <sup>a</sup>	35,955/326,326; 11.02	WI <sup>a</sup>	13,922/162,779; 8.55
KS	80/31,354; 0.26	NC	5,818/253,695; 2.29	WY	8/426; 1.88
Canada, available province/territory data					
AB	1/533; 0.19	NB	61/857; 7.12	ON	1,915/82,886; 2.31
BC	0/180; 0.00	NF	1/146; 0.68	QC	865/22,847; 3.79
MB	621/17,824; 3.48	NS	302/1,523; 19.8	SK	1/36; 2.78

Highlighted states—2017 areas of interest. Also check maps (<http://www.cpcvet.org/parasite-prevalence-maps>. Accessed on January 5, 2018) of adjacent states for high seropositivity in contiguous counties.

<sup>a</sup>Twelve states reported in 2003 to account for 95% of cases.<sup>1</sup>

Subclinical histologic evidence of mild-to-moderate synovial changes and tick bite site perivascularitis and perineuritis are consistent findings in dogs experimentally infected with Bb after tick exposure; the changes seen are milder in 18-week old versus 6-week old exposed puppies.<sup>38,48–50</sup> Although neurologic signs were described in a few seropositive dogs in the past,<sup>51</sup> recent field studies showed no association of neurologic signs in seropositive dogs, thus neuroborreliosis as seen in human and equine<sup>52</sup> patients is not well-documented in dogs.<sup>53–56</sup> Fatal myocarditis was described in Boxer pups with Bb-positive immunohistochemistry, for which no other cause was found;<sup>57</sup> there may be a genetic (breed) predisposition for autoimmune myocarditis triggered by a Lyme antigen which mimics cardiac myosin.<sup>58</sup> Lyme carditis, although uncommon in people, typically is manifested as atrio-ventricular block; this disease presentation also is poorly documented in dogs. Orbital myositis is a rare finding in infected people and has been reported in 1 dog.<sup>59</sup>

Statement: Neurologic and cardiologic manifestations of LB in dogs are not well-documented [EBM-D].

### 3.2 | Topic 2b: European considerations; Bernese Mountain Dogs in Europe

In Europe, numerous serosurveys in dogs from different countries show a wide range of differences in seroprevalence. This is not surprising, considering the unequal distribution of ticks carrying Bb-sl. Little information is available regarding clinical disease in dogs caused by these organisms in Europe. Most studies show no association of seropositivity with clinical signs.<sup>60–64</sup> One clinical study described 98 dogs with clinical signs possibly attributable to LB (history of tick infestation, lameness, neurological signs, nephropathy, lethargy, anorexia, fever).<sup>65</sup> Of these, 21 dogs (21%) were Bb-sl-seropositive (higher seroprevalence than in healthy dogs and dogs showing non-LB clinical signs). In 13 of the 21 dogs, no other cause of illness was found after extensive diagnostic evaluation, indicating a relationship between Bb-sl-seropositivity and disease. However in none of the 13 dogs could spirochetal DNA or viable spirochetes be detected.

Statement: It is not proven that European LB causes clinical signs in dogs [EBM-D].

Interestingly, Bernese Mountain Dogs (BMDs) in Europe are more often Bb-sl-seropositive compared to dogs of other breeds.<sup>60,66</sup> In 1 study, 58% of 160 healthy BMDs were seropositive, compared with 15% seropositivity in healthy dogs of other large breeds with long hair living in the same region.<sup>66</sup> No reason was found as to why the BMDs would be more prone to Bb-sl infection compared to other dogs in the region with similar risk of exposure. In another study of 200 randomly selected dogs admitted to 1 hospital, 13 were BMDs and, of these, 12 (92%) were Bb-sl-seropositive, compared with only 13 (7%) seropositive dogs of the remaining 187 dogs.<sup>60</sup> In this study, BMDs were more often coinfectd with *A. phagocytophilum* but the risk of infection with *A. phagocytophilum* alone was not higher than in other dogs. This finding indicates that a higher exposure of BMDs to ticks could not be the reason for the high Bb-sl-seroprevalence. In both studies, there may have been a breed predisposition of BMDs for Bb-sl infections. Furthermore, it is interesting that both of the studies showing higher Bb-sl-seroprevalence were performed in close proximity to each other in central Europe (Switzerland and southern Germany), the region where the highest prevalence of Bb-sl infested ticks was found.<sup>67</sup> One might speculate about a regional effect, a close genetic relationship among the positive dogs, a genetic predisposition for infection (as was found in Beagles<sup>68</sup>) or a unique infectious species of Bb-sl in the area.

Statement: Although not associated with illness, BMDs in central Europe are more often Bb-sl-seropositive than other breeds [EBM-C].

3.3 | Topic 2c: Considerations in cats

Cats living in Bb-endemic areas are sometimes seropositive.<sup>1,69–73</sup> Cats infested with *I. scapularis* containing Bb develop serum antibodies against the organism and DNA of Bb has been amplified from skin biopsy specimens taken from tick attachment sites.<sup>74–76</sup> Ticks removed

from cats in endemic areas have been positive for Bb.<sup>70</sup> These studies suggest that cats can be infected by Bb and that *Ixodes* spp. are the likely vectors for Bb in cats in the United States.

Cats experimentally infested with *Ixodes* spp. have not developed detectable clinical signs of disease, even if infested twice.<sup>74–76</sup> Cats in Bb-endemic areas may have clinical signs potentially referable to Bb infection but to date, no published studies document the organism as the cause of illness.<sup>69</sup> It is difficult to prove causation of illness associated with Bb in cats because *Ixodes* spp. also are the vector for *A. phagocytophilum*. Anaplasmosis has been documented in cats in 2 studies in a Bb-endemic region.<sup>77,78</sup> Clinical signs of anaplasmosis and borreliosis are similar to each other in dogs and people, and this may be the case for cats as well.

It is proposed by some that cats fail to develop borreliosis because they are more efficient at removing infected ticks. However, seroconversion occurs in naturally exposed and experimentally infested cats suggesting that infection occurs, which should be blocked if ticks were promptly removed. At this time, evidence excluding borreliosis as a cause of clinical illness in cats is as weak as the data indicating causation.

Statement: Although cats may be Bb-seropositive, it is unknown if Bb infection causes illness in cats [EBM-D].

4 | TOPIC 3: WHAT DIAGNOSTIC TESTS TO CONFIRM Bb EXPOSURE ARE RECOMMENDED FOR CLINICALLY ILL ANIMALS?

4.1 | Topic 3a

In dogs, serology is the only recommended modality to evaluate for exposure to Bb (Table 2). Validated serologic tests for Bb exposure in North America include in-house and reference laboratory C<sub>6</sub>-based

TABLE 2 Bb antibody tests available

	Commonly used	Differentiates vaccinal versus natural exposure antibody	Qualitative	Quantitative	Bedside	Differentiates acute versus chronic infection	Heartworm antigen, antibodies to <i>Anaplasma</i> and <i>Ehrlichia</i> spp.
Whole cell IFA or ELISA		No		X			
IgM and IgG		No		X		Possibly	
Western Blot		Possibly	X	Semi		Possibly	
SNAP4DxPlus (IDEXX)	X	Yes, VlsE (C <sub>6</sub> )	X		X		X
Quant C <sub>6</sub> <sup>a</sup> (IDEXX)	X	Yes, VlsE (C <sub>6</sub> )		X			
VetScan Rapid (Abaxis)	X	Possibly; VlsE, OspC, Flagellin	X		X		
AccuPlex4 (Antech)	X	Possibly; OspA, OspC, OspF, p39, SLP	X			Possibly	X
Multiplex (Cornell)	X	Possibly; OspA, OspC, OspF		X		Possibly	

<sup>a</sup>The Quant C<sub>6</sub> is not considered a screening test (see text).



testing (SNAP4Dx and SNAP4DxPlus [IDEXX Laboratories, Westbrook, Maine]; Lyme Quant C6 [IDEXX Laboratories, Westbrook, Maine]),<sup>79–81</sup> the VetScan Canine Lyme Rapid assay (Abaxis North America, Union City, California), the AccuPlex4 test (Antech Diagnostics, Irvine, California),<sup>82,83</sup> and the Multiplex test (Cornell University Animal Health Diagnostic Center, Ithaca, New York).<sup>84,85</sup> Few studies compare different Bb antibody assay performance. In 1 study using Western blot as the gold standard, a commercially available kit based on the C<sub>6</sub> antigen was found to be more accurate than a commercially available multiplex fluorescence (AccuPlex4 [Antech Diagnostics, Irvine, California]) assay.<sup>86</sup> In other studies of dogs experimentally infected with Bb, anti-OspC antibodies were detected before those against other peptides, suggesting that the multiplex assay may be more sensitive in acute cases of LB.<sup>83–85</sup> This may not be clinically relevant because infected dogs do not typically present acutely.<sup>1</sup>

Quantitative Bb antibody assays are available for C<sub>6</sub> (Lyme Quant C6 [IDEXX Laboratories, Westbrook, Maine]), and OspA, OspC, and Osp F antibodies (Multiplex [Cornell University Animal Health Diagnostic Center, Ithaca, New York]). Only 1 panelist recommends the routine use of a quantitative C<sub>6</sub> test for healthy nonclinical, nonproteinuric qualitatively seropositive dogs. The dissenting panelists stated that there is insufficient published evidence that higher titers predict illness or are associated with future illness to advocate routine recommendation of this test in healthy dogs.

Antibodies against C<sub>6</sub>, VlsE (variable major protein-like sequence, expressed), and OspF indicate natural exposure because these antigens are not present in any Bb vaccines. Vaccines that induce OspC antibodies interfere with this marker of natural exposure on Western blot, AccuPlex4, VetScan and Multiplex tests. After experimental natural exposure, OspC antibodies increase by 2–3 weeks, and wane in 3–5 months (without re-exposure), whereas OspF antibodies increase by 6–8 weeks and remain increased in untreated carriers.<sup>83–85,87</sup> The OspC antibodies probably increase again in field conditions (ie, re-exposure is a natural booster), thus finding OspC antibodies in a nonvaccinated dog may indicate recent exposure or re-exposure, without specifying when the dog was first infected in its life. The OspA antibodies usually are a marker for vaccination, but they may develop transiently in early infection,<sup>83,85</sup> or possibly later during chronic infections, as seen in infected humans, because Bb displays antigenic variation, and expresses its antigenic repertoire over time to avoid host immunity.<sup>88–91</sup> The C<sub>6</sub> result has been shown to wane after treatment;<sup>92–94</sup> OspF antibodies also may wane.<sup>95</sup> Determination of quantitative titers to C<sub>6</sub> (or potentially OspF), pre- and 3<sup>94</sup> to 6 months post-treatment, were recommended by 4/6 panelists to check for a decrease after treatment as an indicator of decreased antigenic load, and to establish a new baseline for future comparison, because qualitative tests may stay positive a long time after treatment.<sup>96</sup> An increased result over baseline may indicate re-exposure or relapse. The dissenting panelists state there is no published evidence that quantitative test results predict current illness, the potential for development of chronic disease, or differentiate reinfection from reactivation of a chronic infection.

Panelists did not recommend whole cell ELISA, immunofluorescent antibody (IFA) testing, or Western blot testing because of possible cross-reactions with other spirochetal infections, or the IgM versus IgG antibody testing because dogs do not present with acute illness before seroconversion.<sup>1</sup>

Statement: Panelists agreed that the presence of antibodies against C<sub>6</sub>, VlsE, Osp C (in nonvaccinates), OspF, or some combination of these indicates exposure to Bb, but is not proof of cause of clinical signs, nor can it be used as a predictor for development of future clinical signs [EBM-C].

## 4.2 | Topic 3b

In cats, several studies document antibodies against Bb occur in the serum of cats that are naturally exposed or infected with Bb after being experimentally infested with *I. scapularis*.<sup>70–76</sup> Recent studies measured antibodies against the C<sub>6</sub> peptide using kits labeled for use with dog serum, which do not use species-specific reagents (SNAP4Dx and SNAP4DxPlus [IDEXX Laboratories, Westbrook, Maine]).<sup>75,76</sup> In 2 recent studies in which cats were experimentally infested with wild caught *I. scapularis*, 8 of 13 cats seroconverted.<sup>75,76</sup> Duration of positive test results varied, but was as short as 1 week in 1 cat.<sup>75</sup> In 1 of the studies, skin biopsy specimens also were tested for Bb DNA by PCR assay and 3 of 9 cats were PCR positive but remained C<sub>6</sub> antibody negative over the 84-day study.<sup>76</sup>

Statement: The panel believes that further optimization experiments should be performed before this kit (SNAP4Dx and SNAP4DxPlus [IDEXX Laboratories, Westbrook, Maine]) can be recommended for routine use with cat serum [EBM-D].

## 5 | TOPIC 4: WHAT TREATMENTS ARE RECOMMENDED FOR CLINICALLY ILL ANIMALS?

### 5.1 | Topic 4a: Treatment of lyme arthritis in dogs

The classical presentation of LB is an acute monoarticular or polyarticular lameness with joint swelling, fever, lethargy, and mild local lymphadenopathy,<sup>1</sup> usually in young, often large breed dogs with an active/outdoor lifestyle, but depending upon geographical location, is seen in other types of dogs. Treatment is based on treating infection and managing pain. Experimentally, the illness is self-limiting, and in the field typically a rapid response to antibiotics occurs within 1–2 days.

Many antibiotics, used both parenterally and PO, show efficacy in treating LB (Table 3).<sup>69,98</sup> Beta-lactams and tetracyclines have been shown to be effective for lessening clinical signs of LB in dogs. Because of the protracted biological behavior of *Borrelia*, a long course of antibiotics (4 weeks) is indicated.<sup>95,99–102</sup> The best drug, dosage, and duration of treatment for affected dogs are unknown. Panelists recommend doxycycline as the first choice in most sick dogs with suspected LB because of the ease of administration,

TABLE 3 Antibiotics used in the treatment of LB

Antibiotic	Duration of Use	Frequency	Route	Dosage
Doxycycline or minocycline <sup>a</sup>	30 days	1–2 times daily	PO or IV	10 mg/kg
Amoxicillin	30 days	3 times daily	PO	20 mg/kg
Azithromycin	10–20 days	Once daily	PO	25 mg/kg
Clarithromycin	30 days	2 times daily	PO	7.5–12.5 mg/kg
Erythromycin	30 days	2–3 times daily	PO	25 mg/kg
Cefotaxime	14–30 days	3 times daily	IV	20 mg/kg
Ceftriaxone	14–30 days	Once daily	IV or SC	25 mg/kg
Cefovecin	28 days	2 times, 14 days apart	SC	8 mg/kg

<sup>a</sup>Doxycycline or minocycline are favored choices; minocycline is absorbed better without food.<sup>97</sup>

efficacy against coinfections (eg, *Anaplasma*, *Ehrlichia*, *Leptospira* spp.), and purported antiarthritic, anti-inflammatory properties.<sup>1,103</sup> Doxycycline was not associated with dental staining in children<sup>104</sup> and is labeled for use in puppies and kittens as early as 4 weeks of age in some countries. However, although not a recommendation of the panelists, some veterinarians in the field recommend use of amoxicillin for doxycycline-sensitive or growing dogs. Recently, cefovecin<sup>105</sup> (2 injections, 14 days apart) was shown to be as efficacious as 4 weeks of doxycycline or amoxicillin.<sup>95</sup> Panelists agreed that this option could be considered for dogs intolerant of tetracyclines. Despite reports that 4 weeks of high dose treatment (10 mg/kg doxycycline q12h) did not clear all organisms in all dogs,<sup>101,102</sup> most veterinarians treat for 4 weeks<sup>1</sup> and many use a lower dosage of 10 mg/kg doxycycline q24h or divided q12h. Relapse seen in both dogs and humans<sup>101,102,106–108</sup> may be caused by coinfection or reinfection, especially with other Bb strains.<sup>109</sup>

Chronic Lyme arthritis is not well-documented in dogs and there is no evidence to support treatment beyond 1 month. In humans, the treatment of persistent clinical signs attributed to LB remains controversial (CDC website: <http://www.cdc.gov/lyme/>. Accessed on January 5, 2018; IDSA website: <http://www.idsociety.org/Lyme/>. Accessed on January 5, 2018; ILADS website: <http://www.ilads.org/>. Accessed on January 5, 2018).<sup>91,98,106,108,110,111</sup> A recent randomized, double-blind, placebo-controlled trial in Europe showed no difference in quality of life in those treated short-term versus long-term.<sup>111</sup>

Response to antibiotic treatment in dogs presenting with signs of acute arthritis should be rapid (1–3 days) if the clinical signs are a consequence of LB. Analgesics should be considered (eg, gabapentin for neuropathic pain) as needed. Nonsteroidal anti-inflammatory drugs may be less preferable, so as to avoid a necessary “wash-out” period to decrease risk of gastrointestinal ulceration, should subsequent treatment with glucocorticosteroids be indicated for suspected immune-mediated polyarthropathy in non-responsive dogs. If relapse occurs before or after completion of antibiotic treatment, additional diagnoses should include other infectious disease agents, immune-mediated disease, soft tissue trauma (eg, ligament or meniscal tears), septic arthritis, or degenerative joint disease.<sup>1</sup>

Statement: Panelists agreed that Lyme arthritis be treated for 4 weeks with antibiotics (doxycycline preferred) [EBM-D].

## 5.2 | Topic 4b: Treatment for Bb-seropositive dogs with PLN

The nephropathy putatively associated with borreliosis is an immune-complex glomerulonephritis (ICGN).<sup>112–115</sup> No validated staining techniques are available to prove that glomerular immune complexes found in kidney biopsy specimens are Lyme-specific in the living dog, and diagnosis depends on Bb-seropositivity in a dog with PLN for which no other cause is found. No experimental model for Lyme nephritis is available, and it is difficult to study treatment protocols. Recommendations are based on antimicrobial treatment and standard diagnostic and treatment protocols for ICGN and PLN, as recommended by the IRIS Canine Glomerulonephritis Study Group.<sup>2–5,116–118</sup> Proteinuria concurrent with seropositivity for an infectious agent with the potential to incite glomerular disease does not necessarily document a cause and effect relationship, even if clinical signs (eg, lameness) are seen. Only <30% of dogs with Lyme nephritis have a history of past or concurrent Lyme arthritis.<sup>2,5,51,112</sup> Proteinuria is an uncommon finding, seen in <2% of Bb-seropositive dogs.<sup>119</sup> Antibodies against Bb may be coincidental and a marker for wildlife exposure, because clinical signs (eg, lameness, proteinuria) attributed to LB may be caused by coinfection (eg, *Ehrlichia*, *Anaplasma*, *Babesia*, *Bartonella*, other *Borrelia* spp., Rocky Mountain spotted fever, heartworm, leptospirosis) or tick paralysis. Response to antibiotic treatment also is not proof of causation (eg, doxycycline may treat coinfections and has anti-inflammatory and antiarthritic properties sufficient to cause resolution of clinical signs).<sup>92,99,100,106</sup> Besides infectious causes, PLN may be associated with neoplasia, amyloidosis, as well as genetic, toxic, or other causes. Thus, a thorough diagnostic evaluation still is warranted to rule out other diseases, and to stage and to characterize possible complications of PLN (eg, hypertension, thromboembolic events, nephrotic syndrome, and renal failure).<sup>2,116</sup>

For clinically stable seropositive dogs with mild changes of PLN (ie, uncomplicated nonprogressive renal proteinuria or mild



**TABLE 4** Recommended dosages and adverse effects of representative immunosuppressive drugs for management of immune-complex glomerular disease

Drug	Dosage	Main adverse effects	Mode of action
Mycophenolate <sup>a</sup>	5 mg/kg q12h PO and increase to 10 mg/kg if no GI upset	Gastrointestinal upset	Antagonizes guanosine metabolism
Prednisolone <sup>a</sup>	1mg/kg q12h PO for 4–5 days then taper as soon as possible	Polyuria, polydipsia, polyphagia, thromboembolism, muscle wasting, induction of liver enzymes, panting, adrenal suppression, gastric ulceration	Inhibition of phospholipase A2, reduction in cytokine release, inhibition of neutrophil migration, down regulation of Fc receptor
Azathioprine	2 mg/kg q24h PO for 2 weeks, then 1–2 mg/kg q48h	Gastrointestinal upset, myelosuppression, acute pancreatitis, hepatotoxicity, GI disorders, infection, malignancy	Antagonizes purine metabolism
Cyclosporine	5–20 mg/kg q12h PO (taper dose upward from low to high to avoid GI complications)	Gastrointestinal upset, gingival hyperplasia	Calcineurin inhibitor
Chlorambucil	0.2 mg/kg q24–48h PO	Gastrointestinal upset, myelosuppression	Alkylating agent
Cyclophosphamide	50 mg/m <sup>2</sup> 4 days/week PO, or as pulse treatment 200–250 mg/m <sup>2</sup> every 3 weeks	Myelosuppression, GI upset, hemorrhagic cystitis, infection	Alkylating agent

<sup>a</sup>Mycophenolate is a favored choice, with or without corticosteroids (see text).

hypoalbuminemia, without azotemia) recommendations include antimicrobial treatment, evaluation for evidence of other possible causes of proteinuria (eg, coinfections, neoplasia, genetic diseases), and management of proteinuria, hypertension, and hypercoagulopathy based on established standard-of-care guidelines including a renin-angiotensin-aldosterone system inhibitor (angiotensin-converting enzyme inhibitor or aldosterone receptor (RAAS) blocker), antithrombotics, protein- and phosphorus-restricted diets based on IRIS staging, omega-3 fatty acids, and antihypertensives if needed.<sup>2,3,117</sup> For dogs with more severe, persistent, or progressive glomerular disease, or complications such as vomiting, dehydration, edema, effusions, or worsening azotemia, additional recommendations include antiemetics, crystalloids or colloids, aldosterone antagonist diuretics, phosphate binders, and treatments for chronic kidney disease as needed.<sup>2,3,117</sup> In addition, immunosuppressive agents are indicated if there is biopsy-confirmed evidence of an active immune-mediated pathogenesis (eg, electron-dense deposits by transmission electron microscopy, unequivocal immunofluorescent staining in the glomeruli),<sup>4,120</sup> or even without biopsy confirmation in nonresponders or those with rapid progression, severe azotemia (serum creatinine concentration > 5 mg/dL) or severe hypoalbuminemia (serum albumin concentration < 2.0 g/dL).<sup>2,5,121</sup>

For ICGN with profound proteinuria, hypoalbuminemia, nephrotic syndrome, or rapidly progressive azotemia, single drug or combination treatment consisting of rapidly acting immunosuppressive agents (Table 4) is recommended in addition to antimicrobials and standard PLN treatments and diets.<sup>2–5,117,122,123</sup> Immunosuppressive treatment is not without risk, especially in cases with concurrent diabetes mellitus, pancreatitis, active or latent bacterial or fungal infections, uncontrolled hypertension, hepatic dysfunction, or bone marrow suppression. Another relative contraindication is a breed with known inherited glomerulopathy.

The IRIS Study Group recommended mycophenolate as the first immunosuppressive employed, perhaps with a tapering dose of prednisolone in dogs with acute rapidly progressive glomerular disease.<sup>4</sup> To minimize adverse effects of glucocorticoids, they should not be the sole agent and should be tapered as quickly as possible. Other immunosuppressive drugs (Table 4) are also anecdotally deemed efficacious for ICGN. Experiential evidence suggests that mycophenolate results in more remissions and long-term survival in dogs with ICGN.<sup>4</sup> For stable or slowly progressive glomerular diseases, the Study Group recommended mycophenolate or chlorambucil alone or in combination with azathioprine on alternating days. For mycophenolate-intolerant dogs, consensus was lacking for the next preferred agent. Individual case variation and cost of medication may influence choice of treatment. For situations with extreme financial constraints, a short course of prednisone was suggested (1 mg/kg q12h for 4 days with a 2-week taper).<sup>4</sup>

For both rapidly or slowly progressive forms of ICGN, therapeutic efficacy is assessed serially by monitoring proteinuria, blood pressure, serum albumin concentration, and kidney function tests. In the absence of overt adverse effects, at least 12 weeks of immunosuppressive (non-steroidal) drug treatment should be undertaken before altering or abandoning an immunosuppressive trial. Panelists did not agree on the duration of antibiotic treatment, which ranged from 1 to 3 months, or longer if subsequent Quant C<sub>6</sub> antibody concentrations did not wane appropriately.

Statement: Panelists agreed that Bb-seropositive dogs with PLN be treated with antimicrobials as advised above and that clinicians follow the guidelines for the standard diagnostic tests and treatments for ICGN and PLN as recommended by the IRIS Canine Glomerulonephritis Study Group [EBM-D].

**TABLE 5** Some pros and cons of treatment of all nonproteinuric, nonclinical seropositive dogs

Pros	Cons
Treatment of possible Bb-associated periarticular inflammation	Treatment is not needed if periarticular inflammation is not present; older (18 week old) infected puppies showed milder histologic changes than younger (6 week old) infected puppies
Treatment of possible coinfections	Treatment is not needed if coinfection is not present
Possible prevention of future Lyme arthritis or Lyme nephritis	There is no ability to monitor the response to treatment if the dog is truly nonclinical; the vast majority of Bb-seropositive dogs never become ill nor proteinuric Unnecessary owner cost Overuse of antibiotics may cause microbial resistance in the environment at large Possible adverse effects of treatment Possible laxity in checking for proteinuria in carriers, even though they may not all be cleared with treatment Theoretically, a subclinically infected dog may be in a premunitive state that could be protective, at least for that particular strain

### 5.3 | Topic 4c

Because borreliosis in cats has never been confirmed in a single cat, the optimal treatment plan is unknown. In cats with suspected anaplasmosis, clinical signs rapidly resolve after doxycycline is administered at 5 mg/kg q12h or 10 mg/kg PO q24h for 14–28 days.<sup>77,78</sup> Whether or not these cats also were infected with Bb cannot be determined. Based on studies of acute borreliosis in dogs, these doxycycline protocols are likely to be effective in cats as well.

## 6 | TOPIC 5: WHAT TESTING IS RECOMMENDED FOR HEALTHY ANIMALS?

Panelists (5/5) recommended that a qualitative Bb antibody assay be included with annual wellness and preventive care for healthy dogs living in or near endemic areas in North America (there is no evidence to support screening healthy cats for Bb antibodies). Screening for Bb antibodies allows: (1) follow-up proteinuria screening for all seropositive dogs and early intervention for possible Lyme nephritis (see treatment), (2) follow-up minimal data base including CBC and serum biochemistry to identify cytopenias and kidney disease associated with tick and wildlife exposure, (3) identification of seropositive dogs (sentinels) that may indicate risk of exposure of humans, horses, cats or other dogs in the area and the need for modification of preventive protocols; and, (4) recognition of successful preventive strategies in high risk areas. Panelists identified potential pitfalls when screening healthy dogs, including the potential for overuse of antibiotics in rare dogs with false positive assay results, overuse of antibiotics in healthy dogs that would never develop LB, assay expense, induction of anxiety in the owner, and the additional time necessary for owner education.<sup>1</sup>

Statement: It is recommended to screen all healthy dogs that live in, live near, or travel to Bb-endemic areas in North America for Bb antibodies. It is recommended to screen all Bb-seropositive dogs for proteinuria [EBM-D].

## 7 | TOPIC 6: SHOULD TREATMENTS BE OFFERED FOR NONCLINICAL, NONPROTEINURIC SEROPOSITIVE DOGS?

This topic is still controversial; 4/6 panelists do not routinely recommend treatment for such dogs (Table 5),<sup>96,124</sup> stating that: (1) this practice potentially promotes overuse of antibiotics; (2) no data exists proving treatment of healthy dogs is associated with decreased risk of illness; (3) Bb may not be cleared from all tissues with treatment; and, (4) reinfection may commonly occur in dogs in endemic areas. Seropositivity indicates tick and wildlife exposure and possible coinfection(s). Tick control and possible vaccination should be readdressed (see below). Panelists in North America (5/5) recommend reevaluation for proteinuria at least 2–3 times per year, even if the dog is treated with antibiotics, because clearance may not occur, and because the pathogenesis of Lyme nephritis is unknown.

If a seropositive dog is nonclinical and nonproteinuric, there is no current evidence-based data that a quantitative C<sub>6</sub> antibody test (Lyme Quant C<sub>6</sub> [IDEXX Laboratories, Westbrook, Maine]) result helps decision-making regarding whether antimicrobial treatment is warranted. The magnitude of Quant C<sub>6</sub> is not predictive of illness. A majority of untreated nonclinical nonproteinuric seropositive dogs probably have high concentrations, as do experimentally infected dogs, which all remain nonclinical. In the absence of clinical signs increased Quant C<sub>6</sub> may indicate exposure and a robust immune response to the organism.<sup>96,124</sup> Some dogs may eventually either clear the organism or remain nonclinical carriers, as did experimental dogs.

Dogs that show clinical signs of illness are a small subset of those with high Quant C<sub>6</sub> results. Correlation exists between the magnitude of quantitative C<sub>6</sub> and circulating immune-complex concentration.<sup>114</sup> One panelist recommends that nonclinical dogs with high C<sub>6</sub> results be given a therapeutic course of doxycycline, possibly with a repeat quantitative C<sub>6</sub> performed in 3–6 months to document a new baseline result for comparisons if indicated in the future. Response to treatment is associated with a decrease in Quant C<sub>6</sub>. Evidence is lacking as to what degree of

reduction is considered acceptable as compared with being indication for continued treatment in the absence of clinical signs. The argument for treating until Quant C<sub>6</sub> results wane by at least 50% is that the organism may never be cleared as it enters “protected” collagen tissue, and may develop into a latent cystic or L-form. Clinicians who treat believe treatment may lessen the likelihood of future development of immune-complex disease such as ICGN or nonclinical histologic changes found in experimental dogs (eg, arthritis, perivascularitis, and perineuritis), although this has never been confirmed by a controlled study.

Although anecdotally owners have reported improved well-being after antibiotic treatment in nonclinical dogs, without randomized placebo-controlled clinical trials it is unknown if the perceived improvement is related to decreased subclinical disease from Bb, anti-inflammatory properties, treatment of other subclinical disease, or is merely a placebo effect.

Statement: Most (4/6) panelists do not routinely recommend antimicrobial treatment for nonclinical nonproteinuric Bb-seropositive dogs [EBM-D].

## 8 | TOPIC 7: WHAT PREVENTION MODALITIES ARE RECOMMENDED?

### 8.1 | Topic 7a: Tick control

Prevention of Bb infection and development of LB is multifaceted. The simplest and yet the most difficult step to achieve is tick prevention. Ticks and the wildlife that carry ticks are in ever increasing proximity to dogs and people. Frequent tick checks and removing ticks as soon as they are identified is of utmost importance, although difficult in pets with long or dark hair. Perimeter control is equally important. *Ixodes scapularis* preferentially live under hardwood forest canopy and in the underlying leaf litter.<sup>125–128</sup> At least in the home environment, minimizing chances for tick inhabitation means keeping lawns cut short, cleaning areas of brush and weeds, and using wood chips in gardens. Improved landscaping helps pets avoid ticks questing in vegetation and brush (Centers for Disease Control and Prevention National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) Division of Vector-Borne Diseases (DVBD). Preventing ticks in the yard. [https://www.cdc.gov/lyme/prev/in\\_the\\_yard.html](https://www.cdc.gov/lyme/prev/in_the_yard.html). Accessed on January 5, 2018). Daily tick checks provide timely removal with a hemostat, tweezers, or tick removal device, by grasping the tick close to its attachment on the skin, and retracting slowly but steadily. Kennels should be monitored and treated for *Rhipicephalus* infestations to decrease risk of infection with other tickborne diseases (TBDs). Tick type may be identified by checking for the anal groove of *Ixodes* or with images available on-line (University of Rhode Island at [http://www.tickcounter.org/tick\\_identification](http://www.tickcounter.org/tick_identification). Accessed on January 5, 2018). In Bb-endemic areas, if a person removes an engorged *Ixodes* tick, it is recommended that person take a 1-day dose of doxycycline within 72 hours to help prevent LB.<sup>110</sup> No such study has been done in dogs regarding prevention of LB or other TBDs that are sensitive to doxycycline.

Whether Bb vaccines are used or not, there is strong consensus (6/6) that tick control must be used not only to help prevent LB but also the many other TBDs in Bb-endemic areas for which there are no vaccines available. Because ticks can become active even during the winter if temperature increases above 40°F (4°C),<sup>40</sup> year-round tick prevention is advocated. Many products both topical and oral are available that have label claim against *I. scapularis* and currently are on the market. This panel does not recommend any individual product, but those that quickly kill or prevent attachment and feeding by the tick are preferable. *Borrelia burgdorferi* generally is not transmitted until at least 36–48 hours after tick attachment,<sup>25</sup> but other TBDs may be transmitted more rapidly, and prevention of tick attachment (eg, with amitraz<sup>129</sup> or permethrins<sup>130–134</sup>) or a relatively fast kill after attachment (eg, with isoxazoline products<sup>135–139</sup>) is preferred over use of fipronil, which does not kill the tick until after it has been attached for 24 hours. Fluralaner killed almost 90% of ticks by 4 hours, 98% by 8 hours, and 100% at 12 hours after application.<sup>139</sup> Tick collars should be applied tightly enough to have contact with skin, not just hair. Topical permethrins should not be used on or near cats. The new PO (hydrolysate chewable) isoxazoline products, which kill at least some of the tick species studied to date within 8 hours of attachment by binding to tick-specific neurotransmitter gamma-aminobutyric acid-gated chloride channels which mammals do not have, are easy to administer, increase compliance, and may help coverage for dogs that swim or get bathed often.<sup>140,141</sup> Combinations of products with different mechanisms also may be used. See Table 6 for a comparison of some commonly used tick control products.

In 1 study of 9 cats infested with wild-caught *I. scapularis* twice, 2 cats seroconverted after the first infestation, became seronegative, and then seroconverted again after the second infestation suggesting a new primary infection.<sup>76</sup> Thus, it appears that Bb infection does not induce preventive immunity in cats and repeated infection can occur without tick control. In another study of naturally exposed cats with and without clinical signs referable to borreliosis, whether or not the owner purchased a tick control product was recorded.<sup>142</sup> When serum antibodies against Bb and *A. phagocytophilum* were measured, it was shown that purchase of a tick control product did not lessen the likelihood of detecting serum antibodies. Whether this finding related to lack of efficacy or failure of compliance could not be determined from the study. In dogs, use of tick control products appropriately can lessen the risk of developing antibodies against Bb and *A. phagocytophilum*, and this is likely to occur in cats as well if the products are used as directed.<sup>135,137,143</sup>

Statement: Whether Bb vaccines are used or not, there is strong consensus that tick control must be used not only to help prevent LB but also to prevent many other TBDs for which there are no vaccines available [EBM-C].

### 8.2 | Topic 7b: Bb vaccination

The efficacy of tick control products is excellent, as proven by prevention of seroconversion after tick exposure challenge.<sup>135,137,143</sup> However, compliance for using these products properly is an ongoing problem, and many veterinarians in Bb-endemic areas also recommend

TABLE 6 Examples of tick control products in the United States

Products <sup>a</sup>	T, F	Swim	Cats	Prevents attachment	Age, BW	Pregnancy lactation	Frequency
Topicals							
Fipronil Frontline	T, F	Yes	Yes	No	≥8 week	Consult vet	Monthly
Permethrins Activyl T+ Advantix II Parastar+ Vectra 3D	T, F, M	Yes	No	Yes	≥8 week, 4# ≥7 week, 4#	Consult vet	Monthly
Revolution	Does not kill <i>Ixodes</i> , therefore Revolution is not recommended for tick control						
Collars							
Amitraz Preventic	T only	No	No	Yes	≥12 week	Consult vet	2–3 months
Permethrins Scalibor Seresto	T, F, M	No	No Yes	Yes ≥ 10 week cats	≥12 week ≥7 week, 4#	Consult vet	6 months (2–3 week lag) 8 months
Chewables							
Isoxazolines NexGard Simparica Bravecto <sup>b</sup>	T, F	Yes	No No Topical available	No, but relatively fast kill	≥8 week, 4# ≥6 months	Consult vet Yes	1 month 1 month 3 months; but only 2 months for <i>Amblyomma</i>

BW: body weight; F: fleas; M: mosquitos; T: ticks; wk: weeks; #: pounds.

<sup>a</sup>Products, ingredients, and manufacturers: Activyl Tick Plus (indoxacarb, permethrin; Merck Animal Health, Intervet Inc, Roseland, NJ 07068). Bravecto (fluralaner; Merck Animal Health, Intervet Inc, Summit, NJ 07901). <sup>b</sup>Bravecto topical is available for cats and dogs; oral chewable Bravecto is only available for dogs. Frontline Plus (fipronil, S-methoprene; Merial Limited, Duluth, Georgia 30096). Preventic collar (amitraz; Virbac Corporation, Fort Worth, Texas 76137). K9 Advantix II (imidacloprid, permethrin, pyriproxyfen; Bayer Healthcare LLC, Animal Health Division, Shawnee Mission, Kansas 66201). NexGard (afoxolaner; Frontline Vet Labs, Division of Merial Limited, Athens, Georgia 30601). Parastar Plus for Dogs (fipronil, cyphenothrin; Novartis Animal Health US, Inc, Greensboro North Carolina 27408). Revolution (does not kill *Ixodes*; selamectin; Zoetis Inc, Kalamazoo, Michigan 49007). Scalibor Protector Band (deltamethrin; Merck Animal Health, Intervet Inc, Roseland, New Jersey 07068). Seresto (flumethrin, imidoclopramid; Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, Kansas 66201). Simparica (sarolaner; Zoetis Inc, Kalamazoo, Michigan 49007). Vectra 3D (dinotefuran, permethrin, pyriproxyfen; CEVA US, Lenexa, Kansas 66215).

Bb vaccinations, although the latter are not as efficacious when used alone. In the United States, all currently available Bb vaccines (Recombitek Lyme. Merial Limited. Duluth, Georgia; Lymeavax Zoetis, Florham Park, New Jersey 07932; Duramune Lyme Boehringer Ingelheim Vetmedica, Inc, St. Joseph, Missouri 64506; Nobivac Lyme, Merck Animal Health, Summit, New Jersey 07901; Vanguard crLyme, Zoetis, Florham Park, New Jersey 07932; Table 7) induce anti-OspA antibodies, which when imbibed by a feeding tick will attack spirochetes which express OspA within the tick's midgut, halting transmission. Anti-OspA titers are however not boosted by natural exposure and wane in vaccinates, allowing infection of the host. Anti-OspC antibodies induced by bivalent bacterin vaccines (Lymeavax Zoetis, Florham Park, New Jersey 07932; Duramune Lyme Boehringer Ingelheim Vetmedica, Inc, St. Joseph, Missouri 64506; Nobivac Lyme, Merck Animal Health, Summit, New Jersey 07901) or the chimeric recombinant vaccine (Vanguard crLyme, Zoetis, Florham Park, New Jersey 07932), and boosted by natural exposure, can eliminate transmitted organisms that express OspC. Panelists who routinely recommend Bb vaccines for dogs (in addition to tick control) cite high efficacy, safety, and good duration of immunity

(Jody Sandler, DVM, Director of Veterinary Services. Guiding Eyes for the Blind, Yorktown New York. Personal communication).<sup>144–150</sup> Vaccinal duration of immunity however appears inconsistent and less than ideal for some vaccines studied.<sup>83,151</sup> Six-month boosters have been proposed<sup>147,151</sup> during the initial year (although no safety studies are available) and it is unknown whether or not to suggest 6-month versus annual boosters thereafter. Vaccine failures were found only 22 weeks after OspA subunit or bacterin vaccination.<sup>83</sup> The most recently licensed Bb vaccine (Vanguard crLyme, Zoetis, Florham Park, New Jersey 07932) was shown in prerelease studies to induce OspA and OspC antibodies against 7 Bb strains, which may afford broader protection. In a 15-month duration-of-immunity study completed by the manufacturer, vaccinated dogs were less likely (7/16 dogs seroconverted) than control dogs (14/16 dogs seroconverted) to develop evidence of Bb infection after tick challenge (Zoetis Study B864R-US-12-037).

The routine use of Bb vaccinations in Bb-endemic areas in North America was recommended by 3/6 panelists, for seronegative as well as healthy nonclinical, nonproteinuric seropositive dogs, because no natural immunity occurs from previous infection, partly because of the

TABLE 7 Available Bb vaccines in North America

Vaccine type	Name of vaccine	Adjuvant
Recombinant OspA (monovalent)	Recombitek Lyme (Merial)	No
Bivalent whole-cell inactivated bacterin (contains one Osp A containing strain, one unique OspC-producing strain, as well as other antigens)	LymeVax (Zoetis)	Yes
	Duramune Lyme (Elanco, formerly licensed to Boehringer Ingelheim)	Yes
	Nobivac Lyme (Merck)	Yes
Chimeric recombinant (contains monovalent OspA and 7 types of OspC from North American strains)	Vanguard crLyme (Zoetis)	Yes

ability of the spirochete to “hide” from the immune system in synovial membranes, down-regulating their immunogenic surface proteins,<sup>152</sup> and because of the existence of many strains for which there is no cross-reacting immunity.<sup>99</sup>

The 3/6 panelists who dissented cited inconsistent efficacy and duration of immunity (see above), cost, need for proper tick control, lack of controlled studies with respect to tick control when assessing vaccines in the field, theoretical concerns for immune-mediated sequelae,<sup>1,153</sup> and because most Bb-seropositive dogs remain nonclinical, nonproteinuric carriers. The theoretical concerns regarding future sensitization or aggravation of ICGN by Bb vaccinal antigen-antibody circulating immune complexes (CIC), proinflammatory OspA, or molecular mimicry of other Bb antigens by self-proteins are difficult to study because of the lack of an experimental model of Lyme nephritis, the difficulty in documenting true Lyme nephritis cases in the field, and the probable genetic predisposition whereby Bb immune-complexes are not cleared properly by the kidneys. The evidence for a negative impact of vaccination remains anecdotal at best. It is unknown if there is an underlying genetic podocytopathy,<sup>154</sup> or some other pathogenesis for Lyme nephritis. Fewer than 10% of suspected Lyme nephritis cases had prior Bb vaccination (Richard Goldstein [coauthor]. Personal communication) and their PLN may have been because of other causes (eg, infectious, genetic, amyloidosis, glomerulosclerosis) or vaccine failure. There is no known negative impact of post-vaccinal Lyme-specific CICs, which increase transiently after vaccination ( $\leq 8$  weeks in vaccinated seronegative dogs;

to higher concentrations and longer in vaccinated seropositive dogs).<sup>155,156</sup>

Statement: Panelists agreed that all dogs in Bb-endemic areas (whether vaccinated or not) should receive adequate tick control year-round, preferably with a product that prevents tick attachment or rapidly kills ticks during early feeding. Consensus for vaccination was not reached. Three of 6 panelists recommend vaccination, stating: (1) healthy Bb-seronegative dogs in North American Bb-endemic regions may be vaccinated with any of the currently available Bb vaccines and (2) healthy (nonclinical, nonproteinuric) Bb-seropositive dogs in those regions may be vaccinated if the risk of reinfection is high. It is not recommended to vaccinate sick or proteinuric dogs [EBM-D].

## 9 | SUMMARY

Our panel achieved consensus on evaluating all dogs at risk in North America with a qualitative Bb antibody assay, testing all Bb-seropositive dogs for proteinuria, using doxycycline as the first choice for dogs or cats with suspected clinical LB (although the best protocol and duration are unknown), using mycophenolate with or without prednisone in Lyme nephritis suspects that are not responding to standard care, and using tick control for all dogs and cats at risk (Table 8). Consensus was not reached on whether to treat all Bb-seropositive dogs and cats,

TABLE 8 Summary of recommendations in consensus and not in consensus

Consensus	Nonconsensus
Screening all dogs in Bb-endemic and emerging areas in North America	Treating healthy nonclinical nonproteinuric Bb-seropositive dogs
Testing all Bb-seropositive dogs for proteinuria in North America (frequency/duration debatable)	Using quantitative titers to decide about treatment
Choosing Doxycycline first choice for sick dogs at 10 mg/kg/dy for 1 month	How long to use antibiotics in Lyme nephritis suspects (1 month versus 3–6 months)
Using mycophenolate ( $\pm$ short course prednisone) in Lyme nephritis suspects that are not responding to antibiotics plus standard PLN protocol	Use of Lyme vaccinations
Using tick control for all dogs at risk	6 month boosting of Lyme vaccines



whether to use quantitative C<sub>6</sub> antibody test results to guide treatment recommendations or to follow treatment responses, how long to use antibiotics for Lyme nephritis cases, and whether or not to use Bb vaccines, even in Bb-endemic areas.

### CONFLICT OF INTEREST DECLARATION

The authors declare that none of their collaborations influenced their work on this Consensus. Collaborative Research: Antech Laboratories (MRL), Boehringer Ingelheim Vetmedica, Inc. (REG, MRL, MPL), IDEXX Laboratories (REG, MRL), Zoetis (REG, MRL); Other: AKC-CHF/SCWTCA/SCWTAC (MPL); Grayson-Jockey Club (GEM), Kindy French Foundation (MPL), Maddie's Fund (GEM), NIH (GEM), Shipley Foundation (MAL); Consultant or Sponsored CE events: Aratana (MPL), Boehringer Ingelheim Vetmedica, Inc. (REG, GEM), Heska (MPL), IDEXX Labs (REG, MPL), Merck (REG, GEM), Merial (REG), and Zoetis (REG, MAL, GEM)

### OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

### INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

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### REFERENCES

- [1] Littman MP, Goldstein RE, Labato MA, et al. ACVIM small animal consensus statement on Lyme disease in dogs: diagnosis, treatment, and prevention. *J Vet Intern Med.* 2006;20:422–434. [EBM-D]
- [2] IRIS Glomerular Disease Study Group, Goldstein RE, Brovida C, Fernández-del Palacio MJ, et al. Consensus recommendations for treatment for dogs with serology positive glomerular disease. *J Vet Intern Med.* 2013;27:S60–S66. [EBM-D]
- [3] IRIS Canine GN Study Group Standard Therapy Subgroup, Brown S, Elliott J, Francey T, et al. Consensus recommendations for standard therapy of glomerular disease in dogs. *J Vet Intern Med.* 2013;27:S27–S43. [EBM-D]
- [4] IRIS Canine GN Study Group Established Pathology Subgroup, Segev G, Cowgill LD, Heiene R, et al. Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology. *J Vet Intern Med.* 2013;27:S44–S54. [EBM-D]
- [5] IRIS Canine GN Study Subgroup on Immunosuppressive Therapy Absent a Pathologic Diagnosis, Pressler B, Vaden S, Gerber B, et al. Consensus guidelines for immunosuppressive treatment of dogs with glomerular disease absent a pathologic diagnosis. *J Vet Intern Med.* 2013;27:S55–S59. [EBM-D]
- [6] Cutler SJ, Ruzic-Sabljic E, Potkonjak A. Emerging *borreliæ* - Expanding beyond Lyme borreliosis. *Mol Cell Probes.* 2017;31:22–27. [EBM-D]
- [7] Rhodes DVL, Earnhart CG, Mather TN, et al. Identification of *Borrelia burgdorferi* ospC genotypes in canine tissue following tick infestation: implications for Lyme disease vaccine and diagnostic assay design. *Vet J.* 2013;198:412–418. [EBM-B]
- [8] Brisson D, Baxamusa N, Schwartz I, Wormser GP. Biodiversity of *Borrelia burgdorferi* strains in tissues of Lyme disease patients. *PLoS One.* 2011;6:e22926. [EBM-D]
- [9] Pantchev N, Pluta S, Huisinga E, et al. Tick-borne diseases (Borreliosis, Anaplasmosis, Babesiosis) in German and Austrian Dogs: status quo and review of distribution, transmission, clinical findings, diagnostics and prophylaxis. *Parasitol Res.* 2015;114:S19–S54. [EBM-C]
- [10] Pritt BS, Mead PS, Johnson DK, et al. Identification of a novel pathogenic *Borrelia* species causing Lyme borreliosis with unusually high spirochaetemia: a descriptive study. *Lancet Infect Dis.* 2016;16:556–564. [EBM-D]
- [11] Little SE, Beall MJ, Bowman DD, et al. Canine infection with *Dirofilaria immitis*, *Borrelia burgdorferi*, *Anaplasma* spp., and *Ehrlichia* spp. in the United States, 2010–2012. *Parasit Vectors.* 2014;7:257. [EBM-C]
- [12] Herrin BH, Peregrine AS, Goring J, et al. Canine infection with *Borrelia burgdorferi*, *Dirofilaria immitis*, *Anaplasma* spp. and *Ehrlichia* spp. in Canada, 2013–2014. *Parasit Vectors.* 2017;10:244. [EBM-C]
- [13] Krause PJ, Narasimhan S, Wormser GP, et al. Human *Borrelia miyamotoi* infection in the United States. *N Engl J Med.* 2013;368:291–293. [EBM-D]
- [14] Gugliotta JL, Goethert HK, Berardi VP, Telford SR III. Meningoencephalitis from *Borrelia miyamotoi* in an immunocompromised patient. *N Engl J Med.* 2013;368:240–245. [EBM-D]
- [15] James AM, Liveris D, Wormser GP, et al. *Borrelia lonestari* infection after a bite by an *Amblyomma americanum* tick. *J Infect Dis.* 2001;183:1810–1814. [EBM-D]
- [16] Moyer PL, Varela AS, Luttrell MP, et al. White-tailed deer (*Odocoileus virginianus*) develop spirochetemia following experimental infection with *Borrelia lonestari*. *Vet Microbiol.* 2006;115:229–236. [EBM-D]
- [17] Kelly AL, Raffel SJ, Fischer RJ, et al. First isolation of the relapsing fever spirochete, *Borrelia hermsii*, from a domestic dog. *Ticks Tick Borne Dis.* 2014;5:95–99. [EBM-D]
- [18] Piccione J, Levine GJ, Duff CA, et al. Tick-borne relapsing fever in dogs. *J Vet Intern Med.* 2016;30:1222–1228. [EBM-C]
- [19] Whitney MS, Schwan TG, Sultemeier KB, et al. Spirochetemia caused by *Borrelia turicatae* infection in 3 dogs in Texas. *Vet Clin Pathol.* 2007;36:212–216. [EBM-C]
- [20] Baneth G, Nachum-Biala Y, Halperin T, et al. *Borrelia persica* infection in dogs and cats: clinical manifestations, clinicopathological findings and genetic characterization. *Parasit Vectors.* 2016;9:244. [EBM-C]
- [21] Shirani D, Rakhshanpoor A, Cutler SJ, et al. A case of canine borreliosis in Iran caused by *Borrelia persica*. *Ticks Tick Borne Dis.* 2016;7:424–426. [EBM-D]
- [22] Radolf JD, Caimano MJ, Stevenson B, Hu LT. Of ticks, mice and men: understanding the dual-host lifestyle of Lyme disease spirochaetes. *Nat Rev Microbiol.* 2012;10:87–99. [EBM-C]
- [23] Rollend L, Fish D, Childs JE. Transovarial transmission of *Borrelia* spirochetes by *Ixodes scapularis*: a summary of the literature and recent observations. *Ticks Tick Borne Dis.* 2013;4:46–51. [EBM-C]
- [24] Piesman J, Spielman A. Host-associations and seasonal abundance of immature *Ixodes dammini* in southeastern Massachusetts. *Ann Entomol Soc Am.* 1979;72:829–832. [EBM-C]
- [25] Kidd L, Breitschwerdt EB. Transmission times and prevention of tick-borne diseases in dogs. *Comp Cont Ed.* 2003;25:742–750. [EBM-D]
- [26] Carrade DD, Foley JE, Borjesson DL, Sykes JE. Canine granulocytic anaplasmosis: a review. *J Vet Intern Med.* 2009;23:1129–1141. [EBM-D]

- [27] Hegarty BC, Maggi RG, Koskinen P, et al. *Ehrlichia muris* infection in a dog from Minnesota. *J Vet Intern Med.* 2012;26:1217–1220. [EBM-D]
- [28] Pfeiffer M, Dobler G. Tick-borne encephalitis virus in dogs - is this an issue? *Parasit Vectors.* 2011;4:59. [EBM-D]
- [29] Regier Y, Ballhorn W, Kempf VA. Molecular detection of *Bartonella henselae* in 11 *Ixodes ricinus* ticks extracted from a single cat. *Parasit Vectors* 2017;10:105. [EBM-C]
- [30] Billeter SA, Levy MG, Chomel BB, Breitschwerdt EB. Vector transmission of *Bartonella* species with emphasis on the potential for tick transmission. *Med Vet Entomol.* 2008;22:1–15. [EBM-D]
- [31] Beall MJ, Chandrashekar R, Eberts MD, et al. Serological and molecular prevalence of *Borrelia burgdorferi*, *Anaplasma phagocytophilum*, and *Ehrlichia* species in dogs from Minnesota. *Vector Borne Zoonotic Dis.* 2008;8:455–464. [EBM-C]
- [32] Camacho AT, Guitian FJ, Pallas E, et al. Azotemia and mortality among *Babesia microti*-like infected dogs. *J Vet Intern Med.* 2004;18:141–146. [EBM-C]
- [33] Birkenheuer AJ, Horney B, Bailey M, et al. *Babesia microti*-like infections are prevalent in North American foxes. *Vet Parasitol.* 2010;172:179–182. [EBM-D]
- [34] Hutchinson ML, Strohecker MD, Simmons TW, et al. Prevalence rates of *Borrelia burgdorferi* (Spirochaetales: Spirochaetaceae), *Anaplasma phagocytophilum* (Rickettsiales: Anaplasmataceae), and *Babesia microti* (Piroplasmida: Babesiidae) in host-seeking *Ixodes scapularis* (Acari: Ixodidae) from Pennsylvania. *J Med Entomol.* 2015;52:693–698. [EBM-C]
- [35] Lee X, Coyle DR, Johnson DK, et al. Prevalence of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* in *Ixodes scapularis* (Acari: Ixodidae) nymphs collected in managed red pine forests in Wisconsin. *J Med Entomol.* 2014;51:694–701. [EBM-C]
- [36] Prusinski MA, Kokas JE, Hukey KT, et al. Backenson PB. Prevalence of *Borrelia burgdorferi* (Spirochaetales: Spirochaetaceae), *Anaplasma phagocytophilum* (Rickettsiales: Anaplasmataceae), and *Babesia microti* (Piroplasmida: Babesiidae) in *Ixodes scapularis* (Acari: Ixodidae) collected from recreational lands in the Hudson Valley Region, New York State. *J Med Entomol.* 2014;51:226–236. [EBM-C]
- [37] Koch HG. Seasonal incidence and attachment sites of ticks (Acari: Ixodidae) on domestic dogs in southeastern Oklahoma and northwestern Arkansas, USA. *J Med Entomol.* 1982;19:293–298. [EBM-C]
- [38] Appel MJ, Allan S, Jacobson RH, et al. Experimental Lyme disease in dogs produces arthritis and persistent infection. *J Infect Dis.* 1993;167:651–664. [EBM-B]
- [39] Piesman J, Gern L. Lyme borreliosis in Europe and North America. *Parasitology* 2004;129:S191–S220. [EBM-C]
- [40] Duffy DC, Campbell SR. Ambient air temperature as a predictor of activity of adult *Ixodes scapularis* (Acari: Ixodidae). *J Med Entomol.* 1994;31:178–180. [EBM-C]
- [41] Wood CL, Lafferty KD. Biodiversity and disease: a synthesis of ecological perspectives on Lyme disease transmission. *Trends Ecol Evol.* 2013;28:239–247. [EBM-D]
- [42] Mead PS. Epidemiology of Lyme disease. *Infect Dis Clin North Am.* 2015;29:187–210. [EBM-D]
- [43] Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. *Lancet.* 2012;379:461–473. [EBM-D]
- [44] Estrada-Peña A, Ortega C, Sánchez N, et al. Correlation of *Borrelia burgdorferi* sensu lato prevalence in questing *Ixodes ricinus* ticks with specific abiotic traits in the western palearctic. *Appl Environ Microbiol.* 2011;77:3838–3845. [EBM-C]
- [45] Littman MP. Lyme Disease. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of Veterinary Internal Medicine.* 8th ed. St. Louis: Elsevier; 2017:912–916. [EBM-D]
- [46] Littman MP. Borreliosis. In: Bonagura JD, Twedt DC, eds. *Kirk's Current Veterinary Therapy XV.* St. Louis: Elsevier; 2014:1271–1275. [EBM-D]
- [47] Sykes JE. Lyme Borreliosis. In: Sykes JE, ed. *Canine and Feline Infectious Diseases.* St. Louis: Elsevier; 2014:487–497. [EBM-D]
- [48] Summers BA, Straubinger AF, Jacobson RH, et al. Histopathologic studies of experimental Lyme disease in the dog. *J Comp Pathol.* 2005;133:1–13. [EBM-B]
- [49] Susta L, Uhl EW, Grosenbaugh DA, Krimer PM. Synovial lesions in experimental canine Lyme Borreliosis. *Vet Pathol.* 2012;49:453–461. [EBM-B]
- [50] Grosenbaugh DA, Rissi DR, Krimer PM. Demonstration of the ability of a canine Lyme vaccine to reduce the incidence of histological synovial lesions following experimentally-induced canine Lyme borreliosis. *Vet Immunol Immunopathol.* 2016;180:29–33. [EBM-B]
- [51] Azuma Y, Kawamura K, Isogai H, Isogai E. Neurologic abnormalities in two dogs with suspected Lyme disease. *Microbiol Immunol.* 1993;37:325–329. [EBM-D]
- [52] Johnstone LK, Engiles JB, Aceto H, et al. Retrospective evaluation of horses documented with neuroborreliosis on postmortem examination: 16 cases (2004–2015). *J Vet Intern Med.* 2016;30:1305–1312. [EBM-D]
- [53] Barber RM, Li Q, Diniz PPVP, et al. Evaluation of brain tissue or cerebrospinal fluid with broadly reactive polymerase chain reaction for *Ehrlichia*, *Anaplasma*, spotted fever group *Rickettsia*, *Bartonella*, and *Borrelia* species in canine neurological diseases (109 cases). *J Vet Intern Med.* 2010;24:372–378. [EBM-C]
- [54] Krimer PM, Miller AD, Li Q, et al. Molecular and pathological investigations of the central nervous system in *Borrelia burgdorferi*-infected dogs. *J Vet Diagn Invest.* 2011;23:757–763. [EBM-C]
- [55] Jäderlund KH, Bergström K, Egenvall A, Hedhammar A. Cerebrospinal fluid PCR and antibody concentrations against *Anaplasma phagocytophilum* and *Borrelia burgdorferi* sensu lato in dogs with neurological signs. *J Vet Intern Med.* 2009;23:669–672. [EBM-C]
- [56] Jäderlund KH, Egenvall A, Bergström K, Hedhammar A. Seroprevalence of *Borrelia burgdorferi* sensu lato and *Anaplasma phagocytophilum* in dogs with neurological signs. *Vet Rec.* 2007;160:825–831. [EBM-C]
- [57] Detmer SE, Bouljihad M, Hayden DW, et al. Fatal pyogranulomatous myocarditis in 10 Boxer puppies. *J Vet Diagn Invest.* 2016;28:144–149. [EBM-C]
- [58] Raveche ES, Schutzer SE, Fernandes H, et al. Evidence of *Borrelia* autoimmunity-induced component of Lyme carditis and arthritis. *J Clin Microbiol.* 2005;43:850–856. [EBM-D]
- [59] Raya AI, Afonso JC, Perez-Ecija RA, et al. Orbital myositis associated with Lyme disease in a dog. *Vet Rec.* 2010;167:663–664. [EBM-D]
- [60] Barth C, Straubinger RK, Sauter-Louis C, Hartmann K. Prevalence of antibodies against *Borrelia burgdorferi* sensu lato and *Anaplasma phagocytophilum* and their clinical relevance in dogs in Munich, Germany. *Berl Munch Tierarztl Wochenschr.* 2012;125:337–344. [EBM-C]
- [61] Gerber B, Eichenberger S, Haug K, et al. Association of urine protein excretion and infection with *Borrelia burgdorferi* sensu lato in Bernese Mountain Dogs. *Vet J.* 2009;182:487–488. [EBM-C]
- [62] Gerber B, Haug K, Eichenberger S, et al. Follow-up of Bernese Mountain Dogs and other dogs with serologically diagnosed *Borrelia burgdorferi* infection: what happens to seropositive animals? *BMC Vet Res.* 2009;5:18. [EBM-C]

- [63] Goossens HA, Maes JH, van den Bogaard AE. The prevalence of antibodies against *B. burgdorferi*, an indicator for Lyme borreliosis in dogs? A comparison of serological tests. *Tijdschr Diergeneesk* 2003;128:650–657. [EBM-C]
- [64] Solano-Gallego L, Lull J, Osso M, et al. A serological study of exposure to arthropod-borne pathogens in dogs from northeastern Spain. *Vet Res*. 2006;37:231–244. [EBM-C]
- [65] Speck S, Reiner B, Streich WJ, et al. Canine borreliosis: a laboratory diagnostic trial. *Vet Microbiol*. 2007;120:132–141. [EBM-C]
- [66] Gerber B, Eichenberger S, Wittenbrink MM, Reusch CE. Increased prevalence of *Borrelia burgdorferi* infections in Bernese Mountain Dogs: a possible breed predisposition. *BMC Vet Res*. 2007;3:15. [EBM-C]
- [67] Rauter C, Hartung T. Prevalence of *Borrelia burgdorferi* sensu lato genospecies in *Ixodes ricinus* ticks in Europe: a metaanalysis. *Appl Environ Microbiol*. 2005;71:7203–7216. [EBM-C]
- [68] Contreras E, Moroff S, Lappin M. Evidence for genetic predisposition to *Borrelia burgdorferi* infection in purpose bred beagles. *J Vet Intern Med*. 2016;26:1473. [EBM-C]
- [69] Krupka I, Straubinger RK. Lyme borreliosis in dogs and cats: background, diagnosis, treatment and prevention of infections with *Borrelia burgdorferi* sensu stricto. *Vet Clin North Am Small Anim Pract*. 2010;40:1103–1119. [EBM-D]
- [70] Magnarelli LA, Anderson JF, Levine HR, Levy SA. Tick parasitism and antibodies to *Borrelia burgdorferi* in cats. *J Am Vet Med Assoc*. 1990;197:63–66. [EBM-C]
- [71] Levy SA, O'Connor TP, Hanscom JL, Shields P. Evaluation of a canine C6 ELISA Lyme disease test for the determination of the infection status of cats naturally exposed to *Borrelia burgdorferi*. *Vet Ther*. 2003;4:172–177. [EBM-C]
- [72] Magnarelli LA, Bushmich SL, IJdo JW, Fikrig E. Seroprevalence of antibodies against *Borrelia burgdorferi* and *Anaplasma phagocytophilum* in cats. *Am J Vet Res*. 2005;66:1895–1899. [EBM-C]
- [73] Pantchev N, Vrhovec MG, Pluta S, Straubinger RK. Seropositivity of *Borrelia burgdorferi* in a cohort of symptomatic cats from Europe based on a C<sub>6</sub>-peptide assay with discussion of implications in disease aetiology. *Berl Munch Tierarztl Wochenschr*. 2016;129:333–339. [EBM-C]
- [74] Burgess EC. Experimentally induced infection of cats with *Borrelia burgdorferi*. *Am J Vet Res*. 1992;53:1507–1511. [EBM-B]
- [75] Lappin MR, Chandrashekar R, Stillman B, et al. Evidence of *Anaplasma phagocytophilum* and *Borrelia burgdorferi* infection in cats after exposure to wild-caught adult *Ixodes scapularis* ticks. *J Vet Diagn Invest*. 2015;27:522–525. [EBM-B]
- [76] Lappin MR, Heusken R. *Anaplasma phagocytophilum* and *Borrelia burgdorferi* infections in cats exposed repeatedly to *Ixodes scapularis*. *J Vet Intern Med*. 2015;29:1201. [EBM-B]
- [77] Lappin MR, Breitschwerdt EB, Jensen WA, et al. Molecular and serological evidence of *Anaplasma phagocytophilum* infection of cats in North America. *J Am Vet Med Assoc*. 2004;225:893–896. [EBM-D]
- [78] Savidge C, Ewing P, Andrews J, et al. *Anaplasma phagocytophilum* infection of domestic cats: 16 cases from the northeastern USA. *J Feline Med Surg*. 2016;18:85–91. [EBM-D]
- [79] Chandrashekar R, Mainville CA, Beall MJ, et al. Performance of a commercially available in-clinic ELISA for the detection of antibodies against *Anaplasma phagocytophilum*, *Ehrlichia canis*, and *Borrelia burgdorferi* and *Dirofilaria immitis* antigen in dogs. *Am J Vet Res*. 2010;71:1443–1450. [EBM-C]
- [80] Stillman BA, Monn M, Liu J, et al. Performance of a commercially available in-clinic ELISA for detection of antibodies against *Anaplasma phagocytophilum*, *Anaplasma platys*, *Borrelia burgdorferi*, *Ehrlichia canis*, and *Ehrlichia ewingii* and *Dirofilaria immitis* antigen in dogs. *J Am Vet Med Assoc*. 2014;245:80–86. [EBM-C]
- [81] Gerber B, Haug K, Eichenberger S, et al. Comparison of a rapid immunoassay for antibodies to the C6 antigen with conventional tests for antibodies to *Borrelia burgdorferi* in dogs in Europe. *Vet Rec*. 2009;165:594–597. [EBM-C]
- [82] Caress AL, Moroff S, Lappin MR. *Leptospira* spp. vaccinal antibodies do not react with *Borrelia burgdorferi* peptides used in the AccuPlex 4. *J Vet Diagn Invest*. 2017;29:788–790. [EBM-B]
- [83] Moroff S, Woodruff C, Woodring T, et al. Multiple antigen target approach using the AccuPlex®4 BioCD system to detect *Borrelia burgdorferi* antibodies in experimentally infected and vaccinated dogs. *J Vet Diagn Invest*. 2015;27:581–588. [EBM-B]
- [84] Wagner B, Freer H, Rollins A, Erb HN. A fluorescent bead-based multiplex assay for the simultaneous detection of antibodies to *B. burgdorferi* outer surface proteins in canine serum. *Vet Immunol Immunopathol*. 2011;140:190–198. [EBM-C]
- [85] Wagner B, Freer H, Rollins A, et al. Antibodies to *Borrelia burgdorferi* OspA, OspC, OspF, and C6 antigens as markers for early and late infection in dogs. *Clin Vaccine Immunol*. 2012;19:527–535. [EBM-C]
- [86] Goldstein RE, Eberts MD, Beall MJ, et al. Performance comparison of SNAP®4Dx®Plus and AccuPlex®4 for the detection of antibodies to *Borrelia burgdorferi* and *Anaplasma phagocytophilum*. *Intern J Appl Res Vet Med*. 2014;12:141–147. [EBM-B]
- [87] Callister SM, LaFleur RL, Jobe DA, et al. Antibody responses to *Borrelia burgdorferi* outer surface proteins C and F in experimentally infected Beagle dogs. *J Vet Diagn Invest*. 2015;27:526–530. [EBM-B]
- [88] Guerra MA, Walker ED, Kitron U. Quantitative approach for the serodiagnosis of canine Lyme disease by the immunoblot procedure. *J Clin Microbiol*. 2000;38:2628–2632. [EBM-D]
- [89] Littman MP. Canine borreliosis. *Vet Clin North Am Small Anim Pract*. 2003;33:827–862. [EBM-D]
- [90] Steere AC, Drouin EE, Glickstein LJ. Relationship between immunity to *Borrelia burgdorferi* outer-surface protein A (OspA) and Lyme arthritis. *Clin Inf Dis*. 2011;52:S259–S265. [EBM-D]
- [91] Steere AC, Strle F, Wormser GP, et al. Lyme borreliosis. *Nat Rev*. 2016;2:1–18. [EBM-D]
- [92] Philipp MT, Bowers LC, Fawcett PT, et al. Antibody response to IR6, a conserved immunodominant region of the VlsE lipoprotein, wanes rapidly after antibiotic treatment of *Borrelia burgdorferi* infection in experimental animals and in humans. *J Infect Dis*. 2001;184:870–878. [EBM-C]
- [93] Levy SA, O'Connor TP, Hanscom JL, et al. Quantitative measurement of C6 antibody following antibiotic treatment of *Borrelia burgdorferi* antibody-positive nonclinical dogs. *Clin Vaccine Immunol*. 2008;15:115–119. [EBM-C]
- [94] Chandrashekar R, Beall MJ, Thatcher B, et al. Serologic responses to peptides of *Anaplasma phagocytophilum* and *Borrelia burgdorferi* in dogs infested with wild-caught *Ixodes scapularis*. *Vet J*. 2017; 226:6–11. [EBM-B]
- [95] Wagner B, Johnson J, Garcia-Tapia D, et al. Comparison of effectiveness of cefovecin, doxycycline, and amoxicillin for the treatment of experimentally induced early Lyme borreliosis in dogs. *BMC Vet Res*. 2015;11:163. [EBM-C]
- [96] Littman MP, Goldstein RE. A matter of opinion: should we treat asymptomatic, nonproteinuric Lyme-seropositive dogs with antibiotics? *Clin Brief*. 2011;9:13–16. [EBM-D]
- [97] Hnot ML, Cole LK, Lorch G, et al. Effect of feeding on the pharmacokinetics of oral minocycline in healthy research dogs. *Vet Dermatol*. 2015;26:399–405, e92–93. [EBM-B]



- [98] Wormser GP, O'Connell S. Treatment of infection caused by *Borrelia burgdorferi* sensu lato. *Expert Rev Anti Infect Ther*. 2011;9:245–260. [EBM-D]
- [99] Wormser GP, Schwartz I. Antibiotic treatment of animals infected with *Borrelia burgdorferi*. *Clin Microbiol Rev*. 2009;22:387–395. [EBM-D]
- [100] Levin JM, Nelson JA, Segreti J, et al. *In vitro* susceptibility of *Borrelia burgdorferi* to 11 antimicrobial agents. *Antimicrob Agents Chemother*. 1993;37:1444–1446. [EBM-C]
- [101] Straubinger RK, Summers BA, Chang YF, Appel MJ. Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. *J Clin Microbiol*. 1997;35:111–116. [EBM-C]
- [102] Straubinger RK, Straubinger AF, Summers BA, Jacobson RH. Status of *Borrelia burgdorferi* infection after antibiotic treatment and the effects of corticosteroids: an experimental study. *J Infect Dis*. 2000;181:1069–1081. [EBM-C]
- [103] Kim SE, Kim S, Jeong M, et al. Experimental determination of a subantimicrobial dosage of doxycycline hyclate for treatment of periodontitis in Beagles. *Am J Vet Res*. 2013;74:130–135. [EBM-B]
- [104] Volovitz B, Shkap R, Amir J, et al. Absence of tooth staining with doxycycline treatment in young children. *Clin Pediatr (Phila)*. 2007;46:121–126. [EBM-D]
- [105] Meeus P, Johnson J, Wagner B, et al. Antimicrobial activity of cefovecin (Convenia®) against *Borrelia burgdorferi* and its impact on early Lyme Borreliosis in dogs, in Proceedings. 30th ACVIM Forum 2012. Available at [www.vin.com/members/proceedings/proceedings.plx?CID=ACVIM2012&PID=84302&O=VIN](http://www.vin.com/members/proceedings/proceedings.plx?CID=ACVIM2012&PID=84302&O=VIN). Accessed January 5, 2018. And: a method for treating Lyme disease. Available at [www.google.com/patents/WO2013103531A1?cl=en](http://www.google.com/patents/WO2013103531A1?cl=en). Accessed January 5, 2018. [EBM-B]
- [106] Stricker RB. Counterpoint: long-term antibiotic therapy improves persistent symptoms associated with Lyme disease. *Clin Inf Dis*. 2007;45:149–157. [EBM-D]
- [107] Hodzic E, Imai D, Feng S, Barthold SW. Resurgence of persisting non-cultivable *Borrelia burgdorferi* following antibiotic treatment in mice. *PLoS One*. 2014;9:e86907. [EBM-D]
- [108] Hodzic E. Lyme Borreliosis: is there a preexisting (natural) variation in antimicrobial susceptibility among *Borrelia burgdorferi* strains? *Bosn J Basic Med Sci*. 2015;15:1–13. [EBM-D]
- [109] Nadelman RB, Hanincová K, Mukherjee P, et al. Differentiation of reinfection from relapse in recurrent Lyme disease. *N Engl J Med*. 2012;367:1883–1890. [EBM-D]
- [110] Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med*. 2001;345:79–84. [EBM-D]
- [111] Berende A, ter Hofstede HJM, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *N Engl J Med*. 2016;374:1209–1220. [EBM-D]
- [112] Dambach DM, Smith CA, Lewis RM, Van Winkle TJ. Morphologic, immunohistochemical, and ultrastructural characterization of a distinctive renal lesion in dogs putatively associated with *Borrelia burgdorferi* infection: 49 cases (1987–1992). *Vet Pathol*. 1997;34:85–96. [EBM-C]
- [113] Chou J, Wunschmann A, Hodzic E, Borjesson DL. Detection of *Borrelia burgdorferi* DNA in tissues from dogs with presumptive Lyme borreliosis. *J Am Vet Med Assoc*. 2006;229:1260–1269. [EBM-B]
- [114] Hutton TA, Goldstein RE, Njaa BL, et al. Search for *Borrelia burgdorferi* in kidneys of dogs with suspected “Lyme Nephritis.” *J Vet Intern Med*. 2008;22:860–865. [EBM-B]
- [115] Goldstein RE. Current understanding of Lyme nephropathy. In Proceedings, 25th ACVIM Forum 2007;672–673. [EBM-D]
- [116] IRIS Canine GN Study Group Diagnosis Subgroup, Littman MP, Daminet S, Grauer GF, et al. Consensus recommendations for the diagnostic investigation of dogs with suspected glomerular disease. *J Vet Intern Med*. 2013;27:S19–S26. [EBM-D]
- [117] Littman MP. State-of-the-art-review: Lyme nephritis. *J Vet Emerg Crit Care (San Antonio)*. 2013;23:163–173. [EBM-D]
- [118] Cianciolo RE, Brown CA, Mohr FC, et al. Pathologic evaluation of canine renal biopsies: methods for identifying features that differentiate immune-mediated glomerulonephritides from other categories of glomerular diseases. *J Vet Intern Med*. 2013;27:S10–S18. [EBM-D]
- [119] Goldstein RE, Cordner AP, Sandler JL, et al. Microalbuminuria and comparison of serologic testing for exposure to *Borrelia burgdorferi* in nonclinical Labrador and golden retrievers. *J Vet Diagn Invest*. 2007;19:294–297. [EBM-B]
- [120] Banyard MRC, Hassett RS. The use of mycophenolate mofetil in the treatment of a case of immune-mediated glomerulonephritis in a dog. *Aust Vet Pract*. 2001;31:103–106. [EBM-D]
- [121] O'Neill KE, Labato MA. Immunosuppressive management of twenty-seven proteinuric dogs. Abstract Poster Presentation, Advanced Renal Therapies Symposium, NYC, NY; 2014. [EBM-C]
- [122] Lees GE, Brown SA, Elliot J, et al. Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum consensus statement (small animal). *J Vet Intern Med*. 2005;19:377–385. [EBM-D]
- [123] Littman MP. Protein-losing Nephropathy in Small Animals. In: Acierno MJ, Labato MA, eds. *Kidney Disease and Renal Replacement Therapies*. *Vet Clin N Am (Small Animal)*. 2011;41:31–62. [EBM-D]
- [124] Barr SC. Treating Lyme-seropositive dogs. *Clin Brief Sound Board*. 2012;5:8. [EBM-D]
- [125] Maupin GO, Fish D, Zultowsky J, et al. Landscape ecology of Lyme disease in a residential area of Westchester County, New York. *Am J Epidemiol*. 1991;133:1105–1113. [EBM-C]
- [126] Lindsay LR, Mathison SW, Barker IK, et al. Microclimate and habitat in relation to *Ixodes scapularis* (Acari: Ixodidae) populations on Long point, Ontario, Canada. *J Med Entomol* 1999;36:255–262. [EBM-C]
- [127] Lindsay LR, Mathison SW, Barker IK, et al. Abundance of *Ixodes scapularis* (Acari: Ixodidae) larvae and nymphs in relation to host density and habitat on Long Point, Ontario. *J Med Entomol*. 1999;36:243–254. [EBM-C]
- [128] Schulze TL, Jordan RA, Hung RW. Suppression of subadult *Ixodes scapularis* (Acari: Ixodidae) following removal of leaf litter. *J Med Entomol*. 1995;32:730–733. [EBM-C]
- [129] Elfassy OJ, Goodman FW, Levy SA, Carter LL. Efficacy of an amitraz-impregnated collar in preventing transmission of *Borrelia burgdorferi* by adult *Ixodes scapularis* to dogs. *J Am Vet Med Assoc*. 2001;219:185–189. [EBM-B]
- [130] Endris RG, Cooke D, Amodie D, et al. Repellency and efficacy of 65% permethrin and selamectin spot-on formulations against *Ixodes ricinus* ticks on dogs. *Vet Ther*. 2002;3:64–71. [EBM-B]
- [131] Spencer JA, Butler JM, Stafford KC, et al. Evaluation of permethrin and imidacloprid for prevention of *Borrelia burgdorferi* transmission from blacklegged ticks (*Ixodes scapularis*) to *Borrelia burgdorferi*-free dogs. *Parasitol Res*. 2003;90:S106–S107. [EBM-B]
- [132] Bonneau S, Reymond N, Gupta S, Navarro C. Efficacy of a fixed combination of permethrin 54.5% and fipronil 6.1% (Effitix®) in dogs experimentally infested with *Ixodes ricinus*. *Parasit Vectors*. 2015;8:204. [EBM-B]
- [133] Stanneck D, Kruehwagen EM, Fourie JJ, et al. Efficacy of an imidacloprid/flumethrin collar against fleas and ticks on cats. *Parasit Vectors*. 2012;5:82. [EBM-B]

- [134] Stanneck D, Kruedewagen EM, Fourie JJ, et al. Efficacy of an imidacloprid/flumethrin collar against fleas, ticks, mites and lice on dogs. *Parasit Vectors*. 2012;5:102. [EBM-B]
- [135] Baker CF, McCall JW, McCall SD, et al. Ability of an oral formulation of afoxolaner to protect dogs from *Borrelia burgdorferi* infection transmitted by wild *Ixodes scapularis* ticks. *Comp Immunol Microbiol Infect Dis*. 2016;49:65–69. [EBM-B]
- [136] Mitchell EB, McCall JW, Chester ST, Larsen D. Efficacy of afoxolaner against *Ixodes scapularis* ticks in dogs. *Vet Parasitol*. 2014;201:223–225. [EBM-B]
- [137] Honsberger NA, Six RH, Heinz TJ, et al. Efficacy of sarolaner in the prevention of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* transmission from infected *Ixodes scapularis* to dogs. *Vet Parasitol*. 2016;222:67–72. [EBM-B]
- [138] Six RH, Young DR, Myers MR, Mahabir SP. Comparative speed of kill of sarolaner (Simparica) and afoxolaner (NexGard) against induced infestations of *Ixodes scapularis* on dogs. *Parasit Vectors*. 2016;9:79. [EBM-B]
- [139] Wengenmayer C, Williams H, Zschiesche E, et al. The speed of kill of fluralaner (Bravecto™) against *Ixodes ricinus* ticks on dogs. *Parasit Vectors*. 2014;7:525. [EBM-B]
- [140] Taenzler J, Gale B, Zschiesche E, et al. The effect of water and shampooing on the efficacy of fluralaner spot-on solution against *Ixodes ricinus* and *Ctenocephalides felis* infestations in dogs. *Parasit Vectors*. 2016;9:233. [EBM-B]
- [141] Burgio F, Meyer L, Armstrong R. A comparative laboratory trial evaluating the immediate efficacy of fluralaner, afoxolaner, sarolaner and imidacloprid + permethrin against adult *Rhipicephalus sanguineus* (sensu lato) ticks attached to dogs. *Parasit Vectors*. 2016;9:626. [EBM-B]
- [142] Hoyt K, Chandrashekar R, Breitschwerdt E, Lappin MR. *Anaplasma phagocytophilum* and *Borrelia burgdorferi* antibodies in naturally exposed cats in Maine. *J Vet Intern Med*. 2014;28:1068. [EBM-D]
- [143] McCall JW, Baker CF, Mather TN, et al. The ability of a topical novel combination of fipronil, amitraz and (S)-methoprene to protect dogs from *Borrelia burgdorferi* and *Anaplasma phagocytophilum* infections transmitted by *Ixodes scapularis*. *Vet Parasitol*. 2011;179:335–342. [EBM-B]
- [144] LaFleur RL, Dant JC, Wasmoe TL, et al. Bacterin that induces anti-OspA and anti-OspC borreliacidal antibodies provides a high level of protection against canine Lyme disease. *Clin Vaccine Immunol*. 2009;16:253–259. [EBM-B]
- [145] LaFleur RL, Callister SM, Dant JC, et al. One-year duration of immunity induced by vaccination with a canine Lyme disease bacterin. *Clin Vaccine Immunol*. 2010;17:870–874. [EBM-B]
- [146] Conlon JA, Mather TN, Tanner P, et al. Efficacy of a nonadjuvanted, outer surface protein A, recombinant vaccine in dogs after challenge by ticks naturally infected with *Borrelia burgdorferi*. *Vet Ther*. 2000;1:96–107. [EBM-B]
- [147] Eschner AK, Mugnai K. Immunization with a recombinant subunit OspA vaccine markedly impacts the rate of newly acquired *Borrelia burgdorferi* infections in client-owned dogs living in a coastal community in Maine, USA. *Parasit Vectors*. 2015;8:92. [EBM-C]
- [148] Ball EC. Vanguard crLyme: chimeric recombinant vaccine technology for broad-spectrum protection against canine Lyme disease. *Zoetis Techn Bull*. December 2015. [EBM-B]
- [149] Levy SA, Clark KK, Glickman LT. Infection rates in dogs vaccinated and not vaccinated with an OspA *Borrelia burgdorferi* vaccine in a Lyme disease–endemic area of Connecticut. *Int J Appl Res Vet Med*. 2005;3:1–5. [EBM-C]
- [150] Hebert D, Eschner A. Seroprevalence of *Borrelia burgdorferi*-specific C<sub>6</sub> antibody in dogs before and after implementation of a nonadjuvanted recombinant outer surface protein A vaccine in a Rhode Island small animal clinic. *Vet Ther*. 2010;11:E1–E8. [EBM-C]
- [151] Töpfer KH, Straubinger RK. Characterization of the humoral immune response in dogs after vaccination against the Lyme borreliosis agent: a study with five commercial vaccines using two different vaccination schedules. *Vaccine* 2007;25:314–326. [EBM-B]
- [152] Grimm D, Tilly K, Byram R, et al. Outer-surface protein C of the Lyme disease spirochete: a protein induced in ticks for infection of mammals. *Proc Natl Acad Sci USA*. 2004;101:3142–3147. [EBM-C]
- [153] Littman MP, Goldstein RE. Vaccinating dogs against Lyme disease: two points of view. *Today's Vet Pract*. 2014;4:62–65. [EBM-D]
- [154] Littman MP. Emerging perspectives on hereditary glomerulopathies in canines. *Adv Genomics Genet*. 2015;5:179–188. [EBM-D]
- [155] Goldstein RE, Atwater DZ. Serologic and circulating immune complex analysis in dogs naturally infected with *Borrelia burgdorferi*. *J Vet Intern Med*. 2006;20:713. [EBM-B]
- [156] Goldstein RE, Atwater DZ. Serology and circulating immune complexes in dogs naturally infected with *Borrelia burgdorferi* before and after doxycycline therapy. *J Vet Intern Med*. 2006;20:713. [EBM-B]

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